



AMENDMENTS TO THE SPECIFICATION

A. Please delete the paragraphs appearing at page 5, line 30 through page 6, line 13 (i.e. all of Table 4).

B. Please insert the following at page 45, before Table 5

-- TABLE 4: Polymorphic nucleotide sequences.

51	52	53	54	55	56	57	58	codon position
gga	ggt	ttt	atc	aaa	gta	aga	cag	consensus sequence
GGA	GGT	TTT	ATC	AAA	GTC	AGA	CAA	SEQ ID NO 478
GGA	GGT	TTC	ATT	AAG	GTA	AAA	CAG	SEQ ID NO 479
GGA	GGT	TTT	ATT	AAG	GTA	AGA	CAG	SEQ ID NO 480
GGA	GGT	TTT	ATT	AAA	GTA	AGA	CAA	SEQ ID NO 481
GGA	GGC	TTT	ATC	AAA	GTA	AGA	CAA	SEQ ID NO 482
GGA	GGT	TTT	ATC	AAA	GTC	AGA	CAA	SEQ ID NO 483

78	79	80	81	82	83	84	85	codon position	
gga	cct	aca	cct	gtc	aac	ata	att	gg	consensus sequence
GGA	CCT	ACA	CCG	GTC	AAC	ATA	ATT	GG	SEQ ID NO 484
GGA	CCT	ACA	CCT	GCC	AAT	ATA	ATT	GG	SEQ ID NO 485
GGA	CCT	ACG	CCC	TTC	AAC	ATA	ATT	GG	SEQ ID NO 486
GGA	CCG	ACA	CCT	GTC	ACC	ATA	ATT	GG	SEQ ID NO 487
GGA	CCT	ATA	CCT	GTC	AAC	ATA	ATT	GG	SEQ ID NO 488

87	88	89	90	91	92	93	94	codon position	
a	aga	aat	ctg	ttg	act	cag	att	ggc	consensus sequence
A	AAA	AAT	CTG	ATG	ACT	CAG	ATT	GGC	SEQ ID NO 489
A	AGA	ACT	CTG	TTG	ACT	CAG	CTT	GGA	SEQ ID NO 490
A	AGA	AAT	ATG	ATG	ACC	CAG	CTT	GGC	SEQ ID NO 491
A	AGA	AAT	ATA	ATG	ACT	CAG	CTT	GGA	SEQ ID NO 492
A	AGA	AAT	CTG	CTG	ACT	CAG	ATT	GGG	SEQ ID NO 493
A	AGA	AAT	CTG	TTG	ACA	CAG	CTT	GGC	SEQ ID NO 494

A AGA AAT ATG TTG ACT CAG CTT GGT	SEQ ID NO 495
A AGA AAT TTG TTG ACT CAG ATT GGG	SEQ ID NO 496
A AGA AAT ATG TTG ACT CAG CTT GGT	SEQ ID NO 497
A AGA AAT ATG TTG ACT CAG CTT GGA	SEQ ID NO 498
A AGA AAT CTG TTG ACT CAG CTT GGA	SEQ ID NO 499
A AGA AAC CTG TTG ACT CAA CTT GGT	SEQ ID NO 500--

C. Please amend the paragraphs at page 14, line 27 through page 16, line 18 as follows:

Figure 1: Natural and drug selected variability in the vicinity of codons 30, 46, 48, 50, 54, 82, 84, and 90 of the HIV-1 protease gene. The most frequently observed wild-type sequence is shown in the top line (SEQ ID NO: 520 for codon 30, SEQ ID NO: 521 for codon 46/48, SEQ ID NO: 522 for codon 50, SEQ ID NO: 523 for codon for codon 54, SEQ ID NO: 524 for codon 82/84, and SEQ ID NO: 525 for codon 90). Naturally occurring variations are indicated below and occur independently from each other. Variants sequences for each of the indicated codons are as follows: SEQ ID NO: 7–46 for codon 30, SEQ ID NO: 47–120 for codon 46/48, SEQ ID NO: 121–175 for codon 50, SEQ ID NO: 176–227 for codon 54, SEQ ID NO: 228–357 for codon 82/84, and SEQ ID NO: 358–477 for codon 90. Drug-selected variants are indicated in bold.

Figure 2 A: Reactivities of the selected probes for codon 30 immobilized on LiPA strips with reference material. The information in the boxed surface is not relevant for the discussion of probes for ~~{codon}~~ codon 30. The position of each selected probe on the membrane strip is shown at the left of each panel. The sequence of the relevant part of the selected probes is shown at the left and is given in Table 1. Each strip is incubated with a biotinylated PCR fragment from the reference panel. The reference panel accession numbers are indicated in Table 1 (SEQ ID NO: 31 corresponds to w25, SEQ ID NO: 35 corresponds to w29, SEQ ID NO: 32 corresponds to w32, SEQ ID NO: 42 corresponds to w36, and SEQ ID NO: 29 corresponds to m23). For several probes multiple reference panel possibilities are available, but only one relevant

accession number given each time. *: False positive reactivities. At the bottom the strips, the amino acids at the relevant codon, as derived from the probe reactivity, is indicated.

Figure 2 B: Reactivities of the selected probes for codons 46 and 48 immobilized on LiPA strips with reference material. The information in the boxed surface is not relevant for the discussion of probes for ~~{codons}~~ codons 46 and 48. The position of each selected probe on the membrane strip is shown at the left of each panel. The sequence of the relevant part of the selected probes is given in Table 1. Each strip is incubated with a biotinylated PCR fragment from the reference panel. The reference panel accession numbers are indicated in Table 1 (SEQ ID NO: 93 corresponds to w47, SEQ ID NO: 91 corresponds to w45, SEQ ID NO: 120 corresponds to w72, and SEQ ID NO: 87 corresponds to m41). For several probes multiple reference panel possibilities are available, but only one relevant accession number given each time. *: False positive reactivities. On top of the strips, the amino acids at the relevant codon, as derived from the probe reactivity, is indicated.

Figure 2 C: Reactivities of the selected probes for codon 50 immobilized on LiPA strips with reference material. The information in the boxed surface is not relevant for the discussion of probes for ~~{codon}~~ codon 50. The position of each selected probe on the membrane strip is shown at the left of each panel. The sequence of the relevant part of the selected probes is given in Table 1. Each strip is incubated with a biotinylated PCR fragment from the reference panel. The reference panel accession numbers are indicated in Table 1 (SEQ ID NO: 151 corresponds to w31, SEQ ID NO: 164 corresponds to w44, SEQ ID NO: 172 corresponds to w51, and SEQ ID NO: 157 corresponds to m37). For several probes multiple reference panel possibilities are available, but only one relevant accession number given each time. *: False positive reactivities. At the bottom of the strips, the amino acids at the relevant codon, as derived from the probe reactivity, is indicated.

Figure 2 D: Reactivities of the selected probes for codon 54 immobilized on LiPA strips with reference material. The information in the boxed surface is not relevant for the discussion of probes for ~~{codon}~~ codon 54. The position of each selected probe on the membrane strip is shown at the left of each panel. The sequence of the relevant part of the selected probes is given

in Table 1. Each strip is incubated with a biotinylated PCR fragment from the reference panel. The reference panel accession numbers are indicated in Table 1 (SEQ ID NO: 178 corresponds to w3, SEQ ID NO: 212 corresponds to w34, SEQ ID NO: 189 corresponds to w14, SEQ ID NO: 194 corresponds to w19, SEQ ID NO: 197 corresponds to w22, SEQ ID NO: 202 corresponds to w26, SEQ ID NO: 204 corresponds to w27, SEQ ID NO: 213 corresponds to m35, and SEQ ID NO: 215 corresponds to m37). For several probes multiple reference panel possibilities are available, but only one relevant accession number given each time. *: False positive reactivities. At the bottom of the strips, the amino acids at the relevant codon, as derived from the probe reactivity, is indicated.

Figure 2 E.: Reactivities of the selected probes for codons 82 and 84 immobilized on LiPA strips with reference material. The information in the boxed surface is not relevant for the discussion of probes for ~~{condens}~~ codons 82 and 84. The position of each selected probe on the membrane strip is shown at the left of each panel. The sequence of the relevant part of the selected probes is given in Table 1. Each strip is incubated with a biotinylated PCR fragment from the reference panel. The reference panel accession numbers are indicated in Table 1 (SEQ ID NO: 318 corresponds to w91, SEQ ID NO: 287 corresponds to w60, SEQ ID NO: 338 corresponds to w111, SEQ ID NO: 316 corresponds to w89, SEQ ID NO: 269 corresponds to w42, SEQ ID NO: 263 corresponds to m36, SEQ ID NO: 294 corresponds to m67, SEQ ID NO: 265 corresponds to m38, SEQ ID NO: 332 corresponds to m105, SEQ ID NO: 354 corresponds to m127, SEQ ID NO: 267 corresponds to m40, SEQ ID NO: 290 corresponds to m63, and SEQ ID NO: 328 corresponds to m101). For several probes multiple reference panel possibilities are available, but only one relevant accession number given each time. *: False positive reactivities. At the bottom of the strips, the amino acids at the relevant codon, as derived from the probe reactivity, is indicated.

Figure 2 F: Reactivities of the selected probes for codon 90 immobilized on LiPA strips with reference material. The information in the boxed surface is not relevant for the discussion of probes for ~~{condon}~~ codon 90. The position of each selected probe on the membrane strip is shown at the left of each panel. The sequence of the relevant part of the selected probes is given in Table 1. Each strip is incubated with a biotinylated PCR fragment from the reference panel.

The reference panel accession numbers are indicated in Table 1 (SEQ ID NO: 384 corresponds to w27, SEQ ID NO: 394 corresponds to w37, SEQ ID NO: 396 corresponds to w39, SEQ ID NO: 407 corresponds to w50, SEQ ID NO: 409 corresponds to w52, SEQ ID NO: 426 corresponds to w69, SEQ ID NO: 430 corresponds to w73, SEQ ID NO: 436 corresponds to w79, SEQ ID NO: 400 corresponds to m43, and SEQ ID NO: 413 corresponds to m56). For several probes multiple reference panel possibilities are available, but only one relevant accession number given each time. *: False positive reactivities. At the bottom of the strips, the amino acids at the relevant codon, as derived from the probe reactivity, is indicated.

Figure 3: Sequence and position of the HIV-1 protease amplification primers. To obtain the reactivity with probes selected to determine the susceptibility to antiviral drugs involving codons 30, 46, 48, 50, 54, 82, and 84, nested amplification primers prot2bio(5' primer, SEQ ID NO: 526) and Prot31bio (3' primer, SEQ ID NO: 527) were designed. To obtain the reactivity with probes selected to determine the susceptibility to antiviral drugs involving codon 90, nested amplification primers Prot41bio (5' primer, SEQ ID NO: 528) and Prot6bio (3' primer, SEQ ID NO: 529) were designed.

D. Please amend the paragraph at page 21, lines 15–26, as follows:

It was the aim to adapt all probes to react specifically under the same hybridization and wash conditions by carefully considering the % (G+C), the probe length, the final concentration of the buffer components, and hybridization temperature (Stuyver et al., 1997). Therefore, probes were provided enzymatically with a poly-T-tail using the TdT (Pharmacia) in a standard reaction condition, and purified via precipitation. For a limited number of probes with 3' T-ending sequences, an additional G was incorporated between the probe sequence and the poly-T-tail in order to limit the hybridizing part to the specific probe sequence and to exclude hybridization with the tail sequence. Probe pellets were dissolved in standard saline citrate (SSC) buffer and applied as horizontal parallel lines on a membrane strip. Control lines for amplification (probe 5' TAGGGGGAATTGGAGGTTT TAG 3' (SEQ ID NO: 125), HIV protease aa 47 to aa 54) and conjugate incubation (biotinylated DNA) were applied alongside. Probes were immobilized onto membranes by baking, and the membranes were sliced into 4mm strips also called LiPA strips.

D. Please delete the previously submitted Sequence Listing and replace it with the substitute Sequence Listing enclosed herewith.